

Please amend claims 17, 18, 19, 21, 22, 24, 28, 29, and 32 as indicated in the "mark-up" copy found in Appendix 2 of this Preliminary Amendment. A "clean" copy of the amended claims, in compliance with 37 C.F.R. §1.121, is found in Appendix 3 of this Preliminary Amendment.

REMARKS

The Specification has been amended at page 1, lines 4-7, to replace the existing paragraph with a new paragraph. A "clean" copy of the amendment to the Specification is found in Appendix 1. The Specification has been amended to insert a claim to priority to the parent application of this Divisional application and to remove reference to U.S. Patent Application No. 08/869,426; the claim to the benefit of Application No. 08/869,426 was withdrawn on October 16, 1998 during the prosecution of Application No. 09/089,377. Claims 1-16 have been canceled, and claims 17, 18, 19, 21, 22, 24, 28, 29, and 32 have been amended. A "markup" copy of the amended claims is found in Appendix 2. A "clean" copy of the amended and new claims is found in Appendix 3.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Canceled claims 1-16 were allowed, as amended, in U.S. Patent Application Serial No. 09/089,377. Claims 17, 18, 19, 21, 22, 24, 28, 29, and 32 have been amended to describe the inventive subject matter more clearly. Accordingly, the Examiner

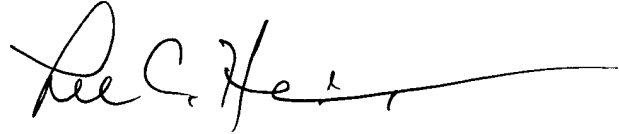
BOX PATENT APPLICATION
Attorney Docket No. 23138A-T

is respectfully requested to enter the above amendments before
examination.

The Examiner is welcomed to telephone the undersigned attorney
if (s)he has any questions or comments.

Respectfully submitted,

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Appendix 1

Amendments to the Specification: clean copy (37 C.F.R.
§1.121(b)(1)).

Please amend the specification by deleting the text at page 1,
lines 4-7, and replacing it with the following:

"This application is a divisional of U.S. Patent Application
No. 09/089,377, filed on June 3, 1998." ^{now 6,274,617}

Appendix 2

Amendments to pending claims: mark-up copy (37 C.F.R. §1.121(c)(ii)).

Please cancel claims 1-16 without prejudice or disclaimer of the subject matter expressed therein.

Please amend claims 17, 18, 19, 21, 22, 24, 28, 29, and 32 as follows:

17. (Once amended) A pharmaceutical composition which comprises:

- (i) an effective amount of a to treat alopecia [heterocyclic ester or amide for treating alopecia or promoting hair growth in an animal; and] nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has a substituent -C(W)-C(Y)- which is attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected from the group consisting of O, S, CH₂, and H₂, and

wherein said compound is additionally substituted with a ester

or amide substituent attached to any atom of the heterocyclic ring
other than said nitrogen atom,

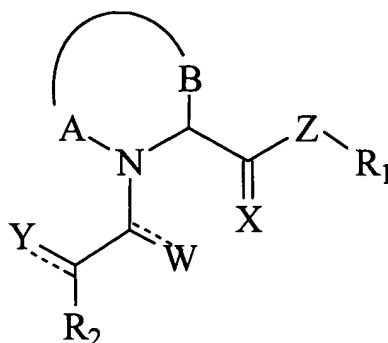
provided that said ester or amide substituent
is not an N-oxide of an ester or amide and
further provided that said amide substituent
is linked to the heterocyclic ring with a
carbon-carbon bond; [and]

- Amide*
- (ii) a second compound for treating alopecia or
promoting hair growth; and
- (iii) a pharmaceutically acceptable carrier.

18. (Once amended) The pharmaceutical composition of claim
17, wherein the [heterocyclic ester or amide] compound is non-
immunosuppressive.

19. (Once amended) The pharmaceutical composition of claim
17, wherein the [heterocyclic ester or amide] compound has an
affinity for an FKBP-type immunophilin.

21. (Once amended) The pharmaceutical composition of claim
17, wherein the [heterocyclic ester or amide is a] compound is of
formula I



or a pharmaceutically acceptable salt, ester, or solvate thereof,

wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO₂, N, NH, or NR₁ heteroatom;

X is O or S;

Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₈ cycloalkyl, and Ar₂;

n is 1 or 2;

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C₁-C₄ straight or branched chain alkyl, C₂-C₄ straight or branched chain alkenyl, and hydroxy; and

Ar₁ and Ar₂ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino[;]_

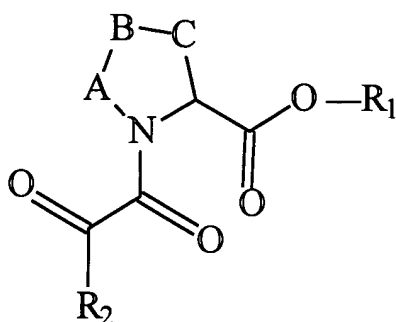
wherein the individual ring size is 5-6 members[;]_

and wherein the heterocyclic ring [contains] has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

22. (Once amended) The pharmaceutical composition of claim 21, wherein [the mono- or bicyclic, carbo- or heterocyclic ring] said Ar₁ or Ar₂ is selected from the group consisting of naphthyl,

indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

24. (Once amended) The pharmaceutical composition of claim 17, wherein the [heterocyclic ester or amide is a] compound is of formula II



II

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B and C are independently CH₂, O, S, SO, SO₂, NH, or NR₁,
provided that A, B and C are not all CH₂;

R₁ is C₁-C₅ straight or branched chain alkyl or C₂-C₅ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n and C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n;

n is 1 or 2;

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, or Ar₁; and

Ar₁ is a an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino[;]L

wherein the individual ring size is 5-6 members[;]L

and wherein the heterocyclic ring [contains] has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

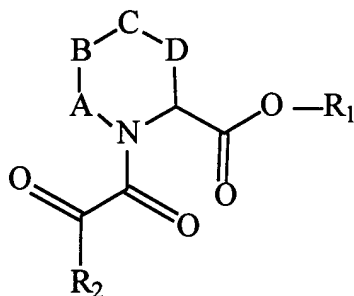
28. (Once amended) The pharmaceutical composition of claim 24, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl(2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate; and

3-(3-pyridyl)-1-propyl(2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate; [and]

or a pharmaceutically acceptable salt[s], ester[s], [and] or solvate[s] thereof.

29. (Once amended) The pharmaceutical composition of claim 17, wherein the [heterocyclic ester or amide is a] compound is of formula III



III

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A, B, C and D are independently CH₂, O, S, SO, SO₂, NH, or NR₁,
provided that A, B, C and D are not all CH₂;

R₁ is C₁-C₅ straight or branched chain alkyl or C₂-C₅ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n and C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n;

n is 1 or 2;

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl, or Ar₁; and

Ar₁ is an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

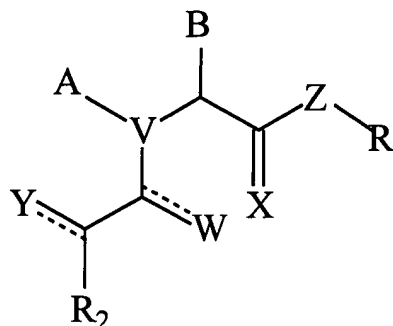
wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino[;]L

wherein the individual ring size is 5-6 members[;]L

and wherein the heterocyclic ring [contains] has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

32. (Once amended) [The pharmaceutical composition of claim 17, wherein the heterocyclic ester or amide is a] A pharmaceutical composition which comprises:

(i) a compound of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof,
wherein:

V is [C, N, or S] CH or N;

A and B, taken together with V and the carbon atom to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO₂, N, NH, and NR;

R is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₉ cycloalkyl, C₅-C₇ cycloalkenyl, or Ar₃,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy,

benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar₄;

Ar₃ and Ar₄ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

wherein the individual ring size is 5-8 members[;],

wherein said heterocyclic ring [contains] has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S; [and

R₁, R₂, W, X, Y, and Z are as defined in claim 21 above.]

X is O or S;

Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₈ cycloalkyl, and Ar₂;

n is 1 or 2; and

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁.

AS wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl
is either unsubstituted or substituted with one or more
substituent(s) independently selected from the group
consisting of C₁-C₄ straight or branched chain alkyl, C₂-
C₄ straight or branched chain alkenyl, and hydroxy;

(ii) a second compound for treating alopecia or promoting

hair growth; and

(iii) a pharmaceutically acceptable carrier.

Appendix 3

Ammendments to pending claims: clean copy (37 C.F.R.
§1.121(c)(ii)).

17. (Once amended) A pharmaceutical composition which
comprises:

(i) an effective amount of a nitrogen-containing heterocyclic
compound having two or more heteroatoms,
wherein said compound has a substituent -C(W)-C(Y)- which is
attached to a nitrogen atom of the heterocyclic ring,

wherein W and Y are independently selected
from the group consisting of O, S, CH₂, and H₂,
and

wherein said compound is additionally substituted with a ester
or amide substituent attached to any atom of the heterocyclic ring
other than said nitrogen atom,

provided that said ester or amide substituent
is not an N-oxide of an ester or amide and
further provided that said amide substituent
is linked to the heterocyclic ring with a
carbon-carbon bond;

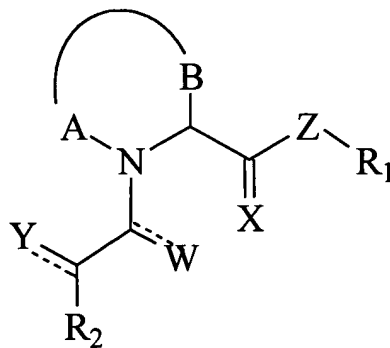
(ii) a second compound for treating alopecia or
promoting hair growth; and

(iii) a pharmaceutically acceptable carrier.

18. (Once amended) The pharmaceutical composition of claim 17, wherein the compound is non-immunosuppressive.

19. (Once amended) The pharmaceutical composition of claim 17, wherein the compound has an affinity for an FKBP-type immunophilin.

21. (Once amended) The pharmaceutical composition of claim 17, wherein the compound is of formula I



I

or a pharmaceutically acceptable salt, ester, or solvate thereof,
wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO₂, N, NH, or NR₁ heteroatom;

X is O or S;

Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₈ cycloalkyl, and Ar₂;

n is 1 or 2;

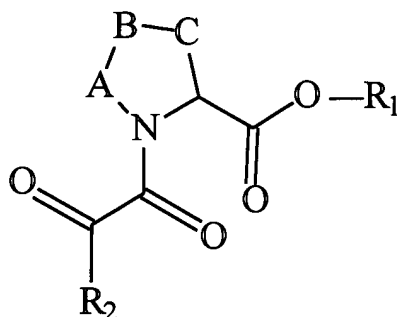
R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C₁-C₄ straight or branched chain alkyl, C₂-

C₄ straight or branched chain alkenyl, and hydroxy; and
Ar₁ and Ar₂ are independently an alicyclic or aromatic, mono-,
bi- or tricyclic, carbo- or heterocyclic ring,
wherein the ring is either unsubstituted or substituted
with one or more substituent(s) independently selected
from the group consisting of halo, hydroxy, nitro,
trifluoromethyl, C₁-C₆ straight or branched chain alkyl,
C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-
C₄ alkenyloxy, phenoxy, benzyloxy, and amino,
wherein the individual ring size is 5-6 members,
and wherein the heterocyclic ring has 1-6 heteroatom(s)
independently selected from the group consisting of O, N,
and S.

22. (Once amended) The pharmaceutical composition of claim
21, wherein said Ar₁ or Ar₂ is selected from the group consisting
of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl,
quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

24. (Once amended) The pharmaceutical composition of claim
17, wherein the compound is of formula II



or a pharmaceutically acceptable salt, ester, or solvate thereof,
wherein:

A, B and C are independently CH₂, O, S, SO, SO₂, NH, or NR₁,
provided that A, B and C are not all CH₂;

R₁ is C₁-C₅ straight or branched chain alkyl or C₂-C₅ straight
or branched chain alkenyl, which is substituted with one or more
substituent(s) independently selected from the group consisting of
(Ar₁)_n and C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight
or branched chain alkenyl substituted with (Ar₁)_n;

n is 1 or 2;

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉
straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇
cycloalkenyl, or Ar₁; and

Ar₁ is a an alicyclic or aromatic, mono-, bi- or tricyclic,
carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted

with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino, wherein the individual ring size is 5-6 members, and wherein the heterocyclic ring has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

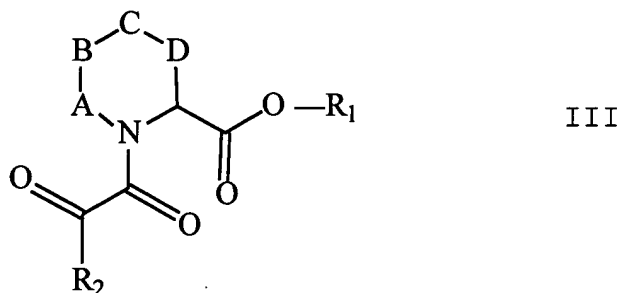
28. (Once amended) The pharmaceutical composition of claim 24, wherein the compound is selected from the group consisting of:

3-phenyl-1-propyl(2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine)carboxylate; and

3-(3-pyridyl)-1-propyl(2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-(4-thiazolidine) carboxylate;

or a pharmaceutically acceptable salt, ester, or solvate thereof.

29. (Once amended) The pharmaceutical composition of claim 17, wherein the compound is of formula III



or a pharmaceutically acceptable salt, ester, or solvate thereof,
wherein:

A, B, C and D are independently CH₂, O, S, SO, SO₂, NH, or NR₁,
provided that A, B, C and D are not all CH₂;

R₁ is C₁-C₅ straight or branched chain alkyl or C₂-C₅ straight
or branched chain alkenyl, which is substituted with one or more
substituent(s) independently selected from the group consisting of
(Ar₁)_n and C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight
or branched chain alkenyl substituted with (Ar₁)_n;

n is 1 or 2;

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉
straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇
cycloalkenyl, or Ar₁; and

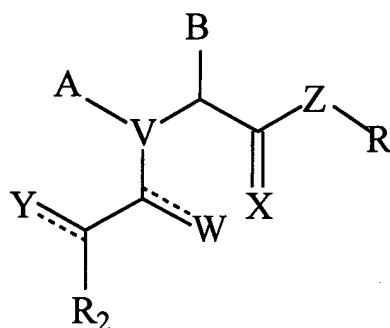
Ar₁ is an alicyclic or aromatic, mono-, bi- or tricyclic,
carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted
with one or more substituent(s) independently selected

from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, and amino, wherein the individual ring size is 5-6 members, and wherein the heterocyclic ring has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

32. (Once amended) A pharmaceutical composition which comprises:

(i) a compound of formula IV



IV

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

V is CH or N;

A and B, taken together with V and the carbon atom to which

they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to V, one or more heteroatom(s) independently selected from the group consisting of O, S, SO, SO₂, N, NH, and NR;

R is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₉ cycloalkyl, C₅-C₇ cycloalkenyl, or Ar₃,

wherein R is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, haloalkyl, carbonyl, carboxy, hydroxy, nitro, trifluoromethyl, C₁-C₆ straight or branched chain alkyl, C₂-C₆ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ alkenyloxy, phenoxy, benzyloxy, thioalkyl, alkylthio, sulfhydryl, amino, alkylamino, aminoalkyl, aminocarboxyl, and Ar₄;

Ar₃ and Ar₄ are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring;

wherein the individual ring size is 5-8 members,

wherein said heterocyclic ring has 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S;

X is O or S;

Z is O, NH, or NR₁;

W and Y are independently O, S, CH₂, or H₂;

R₁ is C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected from the group consisting of (Ar₁)_n, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with (Ar₁)_n, C₃-C₈ cycloalkyl, C₁-C₆ straight or branched chain alkyl or C₂-C₆ straight or branched chain alkenyl substituted with C₃-C₈ cycloalkyl, and Ar₂;

n is 1 or 2; and

R₂ is either C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₃-C₈ cycloalkyl, C₅-C₇ cycloalkenyl or Ar₁,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C₁-C₄ straight or branched chain alkyl, C₂-C₄ straight or branched chain alkenyl, and hydroxy;

- (ii) a second compound for treating alopecia or promoting hair growth; and
- (iii) a pharmaceutically acceptable carrier.